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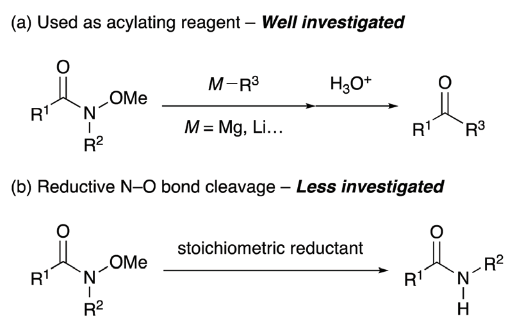
Dealkoxylation of *N*-alkoxyamides without an external reductant driven by Pd/Al cooperative catalysis†

Hirotsugu Suzuki, Takahiro Shiomi, Kenji Yoneoka and Takanori Matsuda *

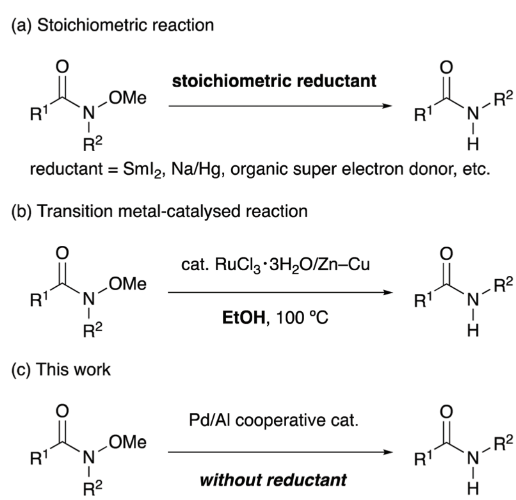
Lewis acid-assisted palladium-catalysed dealkoxylation of *N*-alkoxyamides has been developed. This reaction proceeded smoothly with a range of *N*-alkoxyamides in the absence of an external reductant, thereby establishing a convenient and reductant-free protocol. In addition, a gram-scale reaction could be achieved. Preliminary mechanistic investigations indicated that β-hydrogen elimination from a palladium alkoxide intermediate generated an intramolecular hydride source.

N-Alkoxyamides are an important class of synthetic intermediates for a range of organic transformations.[1] In particular, *N*-methoxy-*N*-methylamides, which are known as Weinreb amides, have unique properties as acylating reagents that suppress the overalkylation of reaction products by forming remarkably stable five-membered cyclic intermediates (Scheme 1a).[2] This exceptional feature allows the transformation of readily available and stable *N*-alkoxyamides[3] into useful aldehydes and ketones in a single step. Recently, *N*-alkoxyamides have emerged as versatile directing groups for C–H bond functionalisation, and various transformations employing *N*-alkoxyamides are currently available.[4] While *N*-alkoxyamides are commonly used in various organic reactions, the dealkoxylation of *N*-alkoxyamides has not been explored enough yet (Scheme 1b).

Conventional dealkoxylation of *N*-alkoxyamides requires stoichiometric metal-based reductants such as SmI_2,[5] Na/Hg[6] and lithium powder[7] (Scheme 2a). An organic, neutral super electron donor has been developed as a stoichiometric reductant, and it gives results comparable to those obtained using metal-based reductants.[8] Base-mediated formal reduction of *N*-alkoxyamides has also evolved as a method for dealkoxylation.[9] Treatment of *N*-alkoxyamides with lithium diisopropylamide,[9a] or *tert*-butyldimethylsilyl triflate and triethylamine[9b] resulted in the formal reduction of the amides, along with the formation of formaldehyde. Although these reductants and bases allow facile cleavage of the alkoxy groups from *N*-alkoxyamides under very mild conditions, excess amounts of reductants or bases are required for these reactions. In



Scheme 1 Transformation of *N*-alkoxyamides: (a) nucleophilic addition of organometallic reagents and (b) dealkoxylation of *N*-alkoxyamides.



Scheme 2 Dealkoxylation of *N*-alkoxyamides.

Department of Applied Chemistry, Tokyo University of Science, 1-3 Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan. E-mail: mtd@rs.tus.ac.jp

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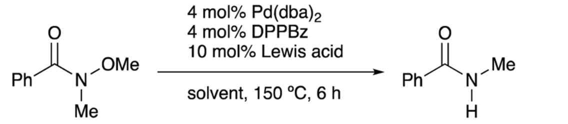
addition, these reducing reagents are sometimes expensive, difficult to handle, and hazardous. Ruthenium-catalysed dealkoxylation of *N*-alkoxyamides has been reported as an alternative protocol for avoiding the use of such stoichiometric reagents (Scheme 2b). Dealkoxylation proceeded in alcoholic solvents, which also behaved as a stoichiometric reductant.[10] Although the catalytic reactions require only green and cheap alcohols as stoichiometric reductants, it is necessary to add a substoichiometric amount of Zn–Cu for activating the ruthenium catalyst. Herein, we report the palladium-catalysed dealkoxylation of *N*-alkoxyamides in the absence of an external reductant as a convenient and reductant-free protocol for dealkoxylation (Scheme 2c). To the best of our knowledge, this is the first report on the catalytic dealkoxylation of *N*-alkoxyamides without any external reductants.[11]

We began our investigation using *N*-methoxy-*N*-methylbenzamide (**1a**) as a model substrate, which was heated in toluene at 150 °C in the presence of the $Pd(dba)_2$/DPPBz catalyst (Table 1). After 6 h, the desired secondary amide **2a** was formed in a moderate yield (entry 1). We then screened aluminium Lewis acids as co-catalysts in order to activate the N–O bond.[12] The addition of aluminium(III) chloride ($AlCl_3$) suppressed the reaction completely (entry 2). Trialkylaluminium or trialkoxyaluminium dramatically improved the yields (entries 3–6), and the best result was obtained when triisobutylaluminium (Al*i*-Bu_3) was employed as a co-catalyst (entry 4).[13] Solvent screening (entries 7–12) revealed that cyclopentyl methyl ether (CPME) was the optimal solvent for affording the desired product in an excellent yield (entry 9).[14] In addition, this demethoxylation reaction could reach completion with reduced catalyst loadings (entry 13).

Table 1 Optimisation of reaction conditions[a]

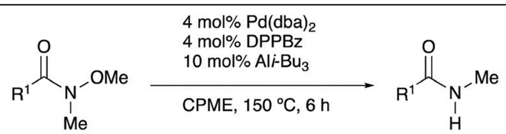


1a **2a**

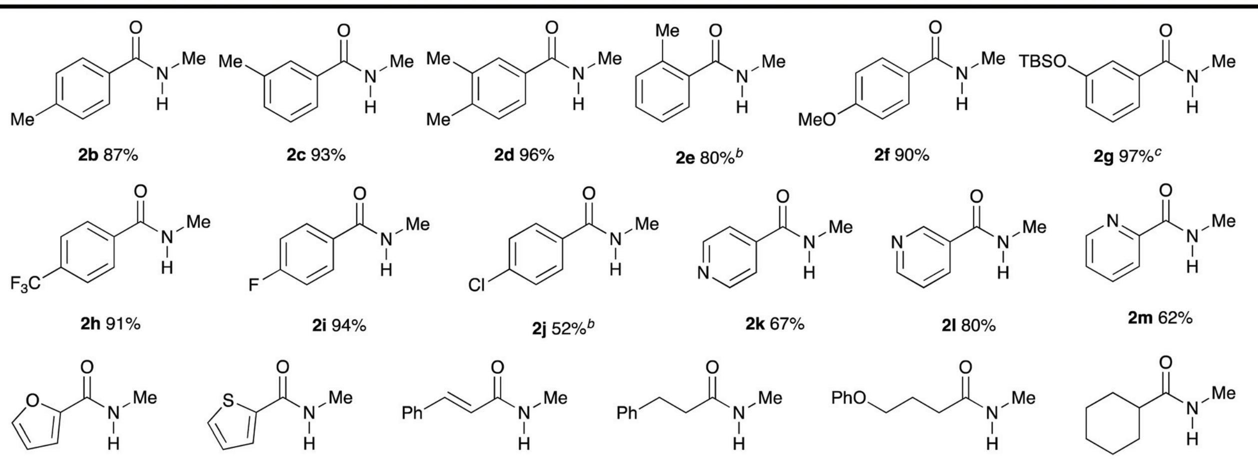
Entry	Lewis acid	Solvent	Yield (%)
1	—	Toluene	33
2	$AlCl_3$	Toluene	NR
3	$AlMe_3$	Toluene	87
4	Al*i*-Bu_3	Toluene	98
5	$Al(OEt)_3$	Toluene	83
6	Al(O*i*-Pr)$_3$	Toluene	94
7	Al*i*-Bu_3	*p*-Xylene	86
8	Al*i*-Bu_3	1,4-Dioxane	86
9	Al*i*-Bu_3	CPME	99
10	Al*i*-Bu_3	Diglyme	85
11	Al*i*-Bu_3	DMF	84
12	Al*i*-Bu_3	DMSO	61
13[b]	Al*i*-Bu_3	CPME	99

[a] Reaction conditions: **1** (0.3 mmol), $Pd(dba)_2$ (4 mol%), DPPBz (4 mol%) and Lewis acid (10 mol%) in CPME (0.3 M) at 150 °C for 6 h, unless otherwise noted. [b] $Pd(dba)_2$/DPPBz (2 mol% each) and Al*i*-Bu_3 (5 mol%) were used as catalysts. The reaction time was 20 h.

Table 2 Palladium-catalysed demethoxylation of *N*-methoxyamides[a]



1 **2**



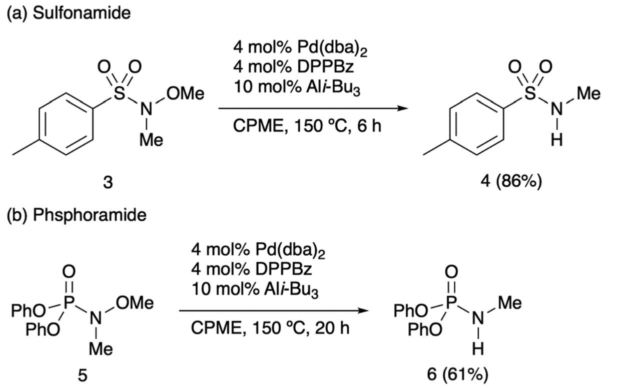
2b 87% **2c** 93% **2d** 96% **2e** 80%[b] **2f** 90% **2g** 97%[c]

2h 91% **2i** 94% **2j** 52%[b] **2k** 67% **2l** 80% **2m** 62%

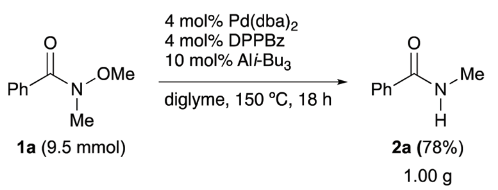
2n 80% **2o** 93% **2p** 70%[b] **2q** 80%[b] **2r** 85%[d] **2s** 79%[b]

[a] Reaction conditions: **1** (0.3 mmol), $Pd(dba)_2$ (4 mol%), DPPBz (4 mol%) and Al*i*-Bu_3 (10 mol%) in CPME (0.3 M) at 150 °C for 6 h, unless otherwise noted. The yields represent the average yield of two reaction runs. [b] $Pd(dba)_2$ (8 mol%), DPPBz (8 mol%) and Al*i*-Bu_3 (20 mol%) were used (20 h). [c] The reaction time was 18 h. [d] $Pd(dba)_2$ (8 mol%), DPPBz (8 mol%) and Al*i*-Bu_3 (20 mol%) were used (18 h).

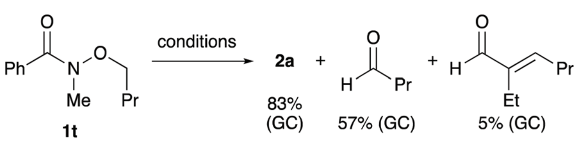
With the optimised reaction conditions in hand, we investigated the scope of demethoxylation (Table 2). Introduction of methyl groups at the *para*- and *meta*-positions of the benzene ring (**1b–d**) did not affect the efficiency of transformations. However, the reactivity decreased with *o*-methylbenzamide **1e**, and increased catalyst loadings were required to obtain a reasonable yield of the desired secondary amide. Benzamides bearing electron-donating and electron-withdrawing groups **1f–j** were well tolerated under the optimal conditions. Heteroaryl-substituted substrates **1k–o** were also converted into the desired secondary amides with high efficiency. Cinnamamide **1p** afforded the corresponding product without the reduction of the olefin moiety.[10] It is worth noting that the demethoxylation of enolisable *N*-methyl-*N*-methoxyamides **1q–s** proceeded smoothly, and no side reactions were observed.



Scheme 3 Palladium-catalysed demethoxylation of sulfonamide **3** and phosphoramidate **5**.



Scheme 4 A gram-scale reaction.

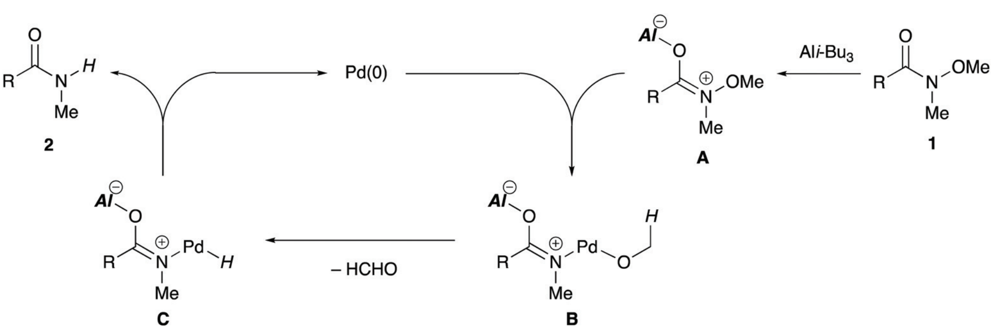


Scheme 5 Palladium-catalysed debutoxylation of *N*-butoxy-*N*-methylbenzamide (**1t**) (conditions: 4 mol% $Pd(dba)_2$, 4 mol% DPPBz, 10 mol% Al*i*-Bu_3, CPME, 150 °C, 6 h).

To further demonstrate the applicability of demethoxylation, other alkoxyamides were examined. Under the optimal conditions, sulfonamide **3** gave the desired secondary sulfonamide **4** in a high yield (Scheme 3a). Moreover, phosphoramidate **5** was found to be a promising substrate for the demethoxylation to afford the corresponding product in a good yield (Scheme 3b). In both cases, an N–O bond was selectively cleaved, while the other heteroatom–heteroatom bonds remained intact. In contrast to previous studies, reductant-free demethoxylation was applicable to a wide range of *N*-methoxy-*N*-methylamides, without the occurrence of any side reactions or over-reactions. Furthermore, a gram-scale reaction was performed with **1a** in diglyme, and the desired product **2a** was obtained in 78% yield (Scheme 4).[15]

To gain insight into the reaction mechanism, a control experiment was conducted (Scheme 5). When *N*-butoxy-*N*-methylbenzamide (**1t**) was subjected to the standard reaction conditions, butanal and its aldol condensation product were produced along with the desired secondary amide **2a**. These byproducts may have been generated *via* the β-hydrogen elimination from a palladium alkoxide intermediate. The results reveal that an α-hydrogen atom with respect to the oxygen atom of the alkoxy group functions as a hydride source.[11,16]

A plausible mechanism for the reductant-free demethoxylation is proposed on the basis of a previous report[11] and our preliminary mechanistic investigations (Scheme 6). The carbonyl oxygen of alkoxyamide **1** coordinates to the aluminium Lewis acid to form **A**, thereby weakening the N–O bond. Subsequently, oxidative addition of the N–O bond to Pd(0) generates palladium alkoxide **B**, which undergoes β-hydrogen elimination to generate palladium hydride intermediate **C** and formaldehyde. Finally, reductive elimination from the intermediate **C** affords secondary amide **2** and simultaneously regenerates the catalytically active Pd(0) species.



Scheme 6 The plausible reaction mechanism for reductant-free demethoxylation.

Conclusions

In summary, we achieved the demethoxylation of *N*-alkoxyamides in the presence of a Pd/Al cooperative catalytic system. The reaction proceeded with various *N*-alkoxyamides including a sulfonamide and a phosphoramide in the absence of an external reductant. The N–O bond was selectively reduced, and there were no side reactions or over-reactions. Preliminary mechanistic investigations revealed that β-hydrogen elimination of a palladium alkoxide intermediate generated an intramolecular hydride source. Further studies on palladium-catalysed reductant-free demethoxylation are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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